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The Attack of the Smart Particles: Should Bacteria Be Afraid?

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ABSTRACT: A shocking state of affairs; the use of nanoparticles as simple carriers is dead and outdated. Stimuli-responsive nanoparticles have emerged as active participants in the therapeutic landscape, rather than inert molecule carriers. And this time they are here to join the ongoing war against an old enemy: bacteria.

Small things considered: we are living in a bacterial world. Bacteria were one of Earth's initial life forms, which emerged at least 3.8 billion years ago. Along with Tardigrades, Earth's most resilient species, bacteria will most likely survive long after humans are gone. Even if our fate is certain, can we at least fight years of evolution and survival?

Bacterial infections constitute a direct threat to human health. Despite the wide use of antibiotics, infection is still one of the leading causes of hospitalization and mortality.[1] This is not due to antibiotics being ineffective but rather due to their low bioavailability and limited penetration to sites of infection.[1] Therefore, antibiotics need to be frequently administered and their half-life is usually an important factor to guide our therapeutic choices. In addition, with the buildup of resistance to present antibiotics and the sluggish development of new pharmaceuticals, alternative methodologies are necessary to avoid a scenario in which all drugs would be rendered ineffective for treating even the most common infections.[2] A possible approach is to pinpoint the drug delivery to and into the bacteria, leading to higher therapeutic efficacy and lower systemic toxicity. Nanomaterials are, in this context, highly attractive as therapeutic delivery vehicles, designed to carry antibiotics to the specific disease sites, while minimally disturbing healthy tissue and cells (Figure 1).[3] This approach has the potential to create new therapies and also gives a new beginning to old ones. Above and beyond, most of the antibiotic resistance mechanisms are irrelevant for nanoparticles since the mode of action of nanoparticles is to promote direct contact with the bacterial wall without the need to penetrate the cell.[4] This raises the hope that nanoparticles would be less prone to promoting resistance in bacteria than regular antibiotics. Therefore, attention has also been focused in the development of nanomaterials with inherent antibacterial activity. In this regard, polymers, metals, and carbon-based materials have been used as a therapeutic strategy in the form of nanoantibiotics.[5] The antimicrobial activity efficacy is attributed not only to the greater surface area to volume ratio but also to the new mechanisms of attacking the microbes.

Our ability to tip the balance toward the beneficial side of the equation has largely been improved by the use of stimuli-responsive nanomaterials.

Nanomaterials possessing a "sense and act" module triggered by cues found in the microbial growth environment are highly advantageous for site-specific delivery of antimicrobial agents.

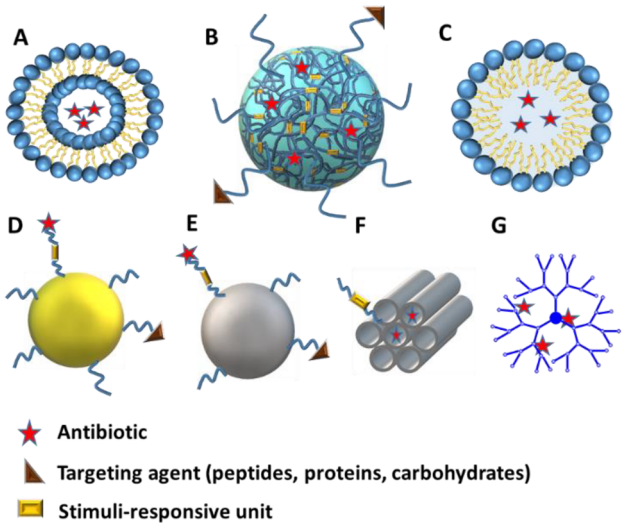

Figure 1. Schematic of nanoparticle-based antimicrobial drug delivery systems: (A) liposome, (B) polymeric nanoparticle, (C) solid lipid nanoparticle, (D) gold nanoparticle, (E) magnetic nanoparticle, and (F) mesoporous silica nanoparticles, and (G) dendrimers.

The most frequently used stimuli are pH, temperature, redox potential, and enzymes.[6] The landscape toward the design of smart nanocarriers is large. There is a toolbox of stimuli-responsive linkers that can be used to incorporate the switch functionality. In addition, chemists have relied upon well-known polymers with inherent stimuli-responsiveness to construct their carriers.[7] Advances in polymer chemistry have allowed us to take major leaps toward more tunable architectures with tailored physical and chemical properties.

pH is one of the most investigated switching triggers. There is a plethora of acid-sensitive bonds and ionizable groups that, through destabilization or decomposition of the nanocarriers, release their payload in response to environmental pH variation. *Helicobacter pylori* or *Vibrio cholera* are examples of bacteria that flourish in an acidic environment. This specificity allows the design of nanoparticles that respond to the pH gradient along the gastrointestinal tract and in cellular compartments. In addition, bacterial infections are often

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associated with acidic pH owing to enhanced metabolic rates due to anaerobic fermentation.

Temperature is a critical environmental trigger for many bacterial species. For example, *Salmonella typhimurium*, *Escherichia coli*, and *Shigella sp*. have been shown to use temperature-dependent environmental signals. This switch has been used to study the mechanism of bacterial adhesion on cell surfaces.[8] The thermoresponsiveness is usually characterized by a sharp phase transition of at least one component of the nanomaterial, through changes in the hydrophobic and hydrophilic balance or disruption of electrostatic interactions.

The construction of nanoscale redox switches is another potential functionality in smart nanomaterials. These are typically built from disulfide groups incorporated in the shell or in the core of the nanoparticle. These bonds are cleaved by glutathione (GSH) in a reductive environment such as that found in the intracellular space. However, the redox environment encountered by intracellular pathogens remains poorly understood, and some pathogens have developed sophisticated mechanisms to sense and adapt to redox stress in the host.[9]

Biomolecules can also be used as triggering motifs. Enzymes provide the most promising stimuli, as enzymatic reactions are highly selective and efficient under mild conditions. As all organisms overexpress certain enzymes (such as proteases, phospholipases, or glycosidases) to help them thrive in their microenvironments, the incorporation of enzyme-responsive functionalities opens up new possibilities to construct next-generation antimicrobial systems with improved efficacy for combating against resistant pathogens. These enzyme-mediated drug delivery systems will promote the accumulation of antibiotics at the desired biological target.

At the infection sites the enhanced permeation and retention (EPR) effect can be used by nanocarriers for passive targeted antibiotic delivery. However, active targeting with bacteria-binding ligands is another strategy to target bacteria.

Cell surface carbohydrates serve as receptors to facilitate cell−cell adhesion for infection by many pathogens. During the past decade, there has been many attempts to integrate carbohydrates in nanomaterials. Stimuli-responsive glyconanoparticles are used as carriers with high affinity and binding specificity due to the multivalent interactions between surface carbohydrate ligands and targeted receptors.[10] In addition, carbohydrates also provide a stealth coating to nanocarriers. At present, only few examples of using glyconanomaterials to deliver antibiotics have been reported in the literature.[11] Therefore, it is expected that this line of research will be much developed in the years to come.

Instead of targeting bacteria, strategies aimed at targeting macrophages are highly attractive as bacteria can survive after having been ingested by phagocytic cells. With this mechanism, bacteria can actually protect themselves against the bactericidal action of antibiotics, which leads to further infection recurrence. Macrophages express high levels of the mannose receptor; thus, by combining the targeting efficiency of small molecules such as mannose with stimuli-responsive units, multifunctional responsive nanomaterials can be built.

Dynamic covalent bonds are another interesting approach in the design of stimuli-responsive nanoparticles. These bonds has been recently applied to prepare single-chain polymer nanoparticles that can undergo intra- to interpolymer chain crosslinking into a polymeric film.[12] This method could potentially be applied to surfaces displaying molecular recognition motifs, such as bacterial surfaces.

In conclusion, the field of stimuli-responsive nanoparticles applied against bacteria is still in its infancy, but it have great potential to improve our survival rate. From nanoantibiotics, stimuli-responsive nanoparticles, friendly glyconanoparticles to the possibility of "wrapping" a bacteria, our hopes dictate that we can at least match the war.

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Notes

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